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Treatment Outcomes for Hepatoblastoma: A 10 Year Retrospective Review at Sheikh Khalifa Medical City

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Abstract

Introduction: *Hepatoblastoma is the most common malignant liver tumor in children. The treatment approach for hepatoblastoma varies from center to center. In our center, we have adopted the Children's Oncology Group AHEP0731 protocol that advocates for pre-operative chemotherapy. In addition, we have tried some experimental regimens for relapsed solid tumors on patients who failed standard therapy by progressing while on treatment, or by disease recurrence with distant metastases.*

Objectives: *To investigate the outcome of the current treatment protocols at Sheikh Khalifa Medical City (SKMC) and determine its prognostic significance. Methods: A cross-sectional, retrospective review of Electronic Medical Records (EMR), of children 0-16 who were evaluated at SKMC, the largest tertiary pediatric hospital in UAE, during the period of Jan 2009 – Oct 2019. We reviewed the clinical presentation, serum α-fetoprotein level at diagnosis, histological subtype, treatment, and outcomes.*

Results*: A total number of 14 patients were included in the study after applying inclusion criteria. There were 6 males (42.9%) and 8 females (57.1%) with a median age of 26.86 months between January 2009 and October 2019. Of the 14 patients, 11 patients (78.6%) were symptomatic at time of diagnosis, with abdominal mass being the most common presenting complains in 35%. Eight patients (57.1%) presented as stage 3 tumor as per the PRETEXT staging system. Epithelial histopathological subtype was predominant in 11 out of the 14 patients 78.6%. Only one case was Pure Fetal type with multifocal involvement of the liver. 12 patients have received preoperative chemotherapy, followed by surgical resection; only one patient underwent upfront surgical resection followed by chemotherapy. preoperative chemotherapy consists of 2 to 4 cycles of Cisplatin, Fluorouracil, Vincristine and Doxorubicin (C5VD), followed by surgical resection. Four of them underwent neoadjuvant experimental chemotherapy utilizing agents such as Pazopanib, Pembrolizumab and Sorafenib. During follow-up, six patients died of progressive disease. The median survival time was 42 months (95% confidence interval: 18–42%). Five-year overall survival was 44.09% (95% confidence interval: 18–42%).*

Conclusion(s): *In conclusion, the combination of surgery and chemotherapy for Hepatoblastoma is an effective approach. The potential effect of neoadjuvant chemotherapy on hepatoblastoma might facilitate remission and convert unresectable tumors into operable ones. Utilization of new-targeted therapies and relapsed sold tumors regimens may prolong the life of those patients with advanced disease who fail to show response to conventional or standard therapy. Further studies on those regimens are required to validate its usage on patients with advanced hepatoblastoma.*

Background

Hepatoblastoma (HB) is one of the most common malignant liver tumors in children; it accounts for 50% of all liver tumors and 1.3% of malignant tumors in children [1].

In majority of cases, it affects those who are two years of age and younger, and it's rarely seen in those older than 5 years of age. The incidence of hepatoblastoma is twice more in males than that in females. Certain syndromes carry a higher risk of genetic predisposition to hepatoblastoma such as Beckwith Wiedmann syndrome, trisomy 18, trisomy 21, Acardia syndrome, Li-Fraumeni syndrome, Goldenhar syndrome, type 1a glycogen storage disease (von Gierke disease), and familial adenomatous polyposis (FAP) [2]. Majority of patients present with an abdominal mass, most commonly involving the right lobe of liver than the left, in 20-30 of patients bilobar involvement is seen, while multicentric involvement account for 15% 3,4, other symptoms can be vague and present like any other liver illness such as anorexia, weight loss and abdominal pain [3]. The serum level of alpha-fetoprotein (AFP) is almost always elevated. Bilirubin and liver enzymes are usually normal [4]. 10% to 20% of patients present with distant metastases at diagnosis, with lungs being the commonest site of metastasis, other rare sites of distant metastasis includes brain and bone. Hepatoblastoma histologically classified as epithelial (56%) or mixed epithelial/mesenchymal (44%) [5]. Epithelial type is subdivided to pure fetal (31%) which carried the best prognosis, embryonal (19%), macro trabecular (3%) and small-cell undifferentiated (SCU) (3%) which is the worst in terms of prognosis. While mixed consists of stromal derivatives and teratiod [6].

The mainstay of curative therapy in children with hepatoblastoma is surgical resection, however only one- third to one – half of the newly diagnosed patients present with a fully resectable disease, those patients have an excellent prognosis (90% event-free survival [EFS]). The main factors that contribute to the clinical outcome in patients with hepatoblastoma depend on the presence or absence of metastatic disease and tumor resectability [7].

In addition, to the histological type of hepatoblastoma, such as SCU histology, which is shown to be of the worst prognosis as previously stated [8,9]. Multiple studies from around the world in the last 3 decades have demonstrated the effectiveness of chemotherapy in increasing rates of surgical resection and survival in initially unresectable patients.[10,11]

Chemotherapy enhanced the survival of those patients with unresectable hepatoblastoma, as it increases the chances of rendering the tumor resectable [10]. However, more recent trials in the last decade have failed to significantly improve survival numbers. Therefore, the current EFS for the entire group of patients with non-metastatic, and unresectable hepatoblastoma at diagnosis remains

suboptimal (< 70%) and warrants novel treatment approaches. The survival of patients with metastatic disease at diagnosis remains poor (20-30%) and also requires consideration of novel therapeutic strategies.[7,10]

Different chemotherapy agents have previously been tried, Cisplatin (CDDP) is known to be the most active agent for the treatment of hepatoblastoma.[12, 13] Followed by Doxorubicin (DOXO). Little is known about the efficacy of other single agents such as Ifosfamide (IFOS), Etoposide (ETOP), Vincristine (VCR), 5-Fluorouracil (FU), Cyclophosphamide (CPM), and Carboplatin (CARBO) in the treatment of hepatoblastoma as most of these agents have been used in combination.10,14 The decrease of AFP levels after 4 cycles of chemotherapy and prior to surgical resection of the tumor has been shown to have prognostic value.[16] However, it's not clear if the initial rate of decline or the magnitude of decline of AFP after each cycle of chemotherapy can be used to guide subsequent therapy. Initial AFP < 100 ng/mL has been associated with an adverse outcome and worse prognosis.

The recent trends of upfront preoperative chemotherapy followed by surgical resection have increase resectability, and decrease surgical morbidity associated with resection, however it increased the amount of chemotherapy received by the patients and resulted in increased short-term and long-term toxicity.

In SKMC, we have adopted the AHEP0731 protocol that is based on the results of the last 20 years of hepatoblastoma clinical trials and seeks to diminish toxicity and improve survival.

Subjects and Methods

In an attempt to minimize surgical risk and associated comorbidities, SIOPEL-1 introduced the pretreatment extent of disease PRETEXT system to define the liver involvement by the tumor [15]. It aims to predict surgical resectability and prognosis.

Patients

We retrospectively reviewed and analyzed a comprehensive set of data obtained from electronic medical records of children who were admitted with a confirmed diagnosis of Hepatoblastoma in SKMC in Abu-Dhabi, UAE from January 2009 to October 2019.

Our objective was to review the experience of a leading tertiary referral center in treating hepatoblastoma in children over the past 10 years.

Eligible subjects were identified using relevant diagnosis based on international classification of disease (ICD-9&10) E-codes. The inclusion criterion was children under 16 years of age with newly diagnosed hepatoblas¬toma who had never received treatment prior to the study period.

Exclusion criteria included patients outside of the specified age range and those diagnosed or managed in a different institute prior being under our care. Out of the 16 patients, diagnosed with hepatoblastoma, only 14 qualified as per our inclusion criteria to studies. 2 patients excluded, as they were diagnosed and managed in another facility, and came for follow up at SKMC.

Methods

The initial diagnosis of hepatoblastoma could have been made either through a tissue pathology or by clinical diagnosis such as elevated AFP level, and tumor evidence by imaging studies. However, all patients must have had a tissue pathology to confirm the diagnosis of hepatoblastoma, which was confirmed in all 14 patients included in this study. As per our treatment guidelines, all patients must be initially evaluated by a pediatric surgeon and received upfront surgery if the tumor is found to be resectable. For those who had an unresectable tumor, 2-4 courses of neoadjuvant chemotherapy were given before a reevaluation. After surgery, adjuvant chemotherapy was given until the AFP level was reported to return to normal on 2 consecutive occasions, along with evidence of tumor regression on radiological imaging.

Staging and Histologic Classification

Cohort was classified according to the Children's Cancer Group (CCG) and the Pre-Text staging system (Table-1). There were 4 stages: stage I, complete

Table -1. The PRETEXT Staging of hepatobastoma

Stage	U.S. Intergroup	SIOP
I	Completely resected	3 adjacent sectors free
II	Microscopic residual	2 adjacent sectors free
III	Macroscopic residual, unresectable or rupture of capsule	2 non-adjacent sectors or 1 sector free
IV	Metastatic	No free sectors

surgical resection with margin free from tumor; stage II, gross resection with microscopic residual disease; stage III, gross resection with macroscopic residual disease; and stage IV, distant metastases. Histologic subtypes included epithelial (embryonal, fetal, mixed fetal and embryonal type), mesenchymal or mixed epithelial, and mesenchymal type.

All patients with Stage I pure fetal histology (PFH) hepatoblastoma were classified as very low-risk and underwent full surgical resection only.

Patients with Stage I non-PFH, non-small cell undifferentiated (SCU) hepatoblastoma or with Stage II non-SCU hepatoblastoma will be classified as low-risk and will be treated on Regimen T with 2 adjuvant cycles of cisplatin, 5-flouorouracil, and vincristine (C5V). Patients with Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma will be classified as intermediate-risk and will be treated with Regimen F, which includes 6 cycles of C5V plus Doxorubicin, followed by surgical resection of the tumor. Surgical resection is intended after 4 cycles of intermediate- risk therapy. All patients with any Stage IV hepatoblastoma as well as patients with any stage of hepatoblastoma and initial AFP <100 ng/mL will be classified as high-risk and will be treated with the novel combination of Vincristine, Irinotecan in regimen H which consists of 2 cycles of "up-front" Vincristine, Irinotecan in the initial 6 weeks of therapy. Patients who respond to Vincristine/Irinotecan (VI) will continue to receive this combination. Serum AFP and image studies including abdominal ultrasonography and/or computed tomographic scan were regularly examined to evaluate treatment response. Heart echocardiogram and hearing test were examined to detect possible sequelae. Temsirolimus was not utilized for Regimen H patients, as it is not available in our institution.

Statistical analysis

Overall survival (OS) was defined as duration between the date of diagnosis and the death or the latest follow-up. Event-free survival (EFS) was defined as the interval from the date of diagnosis to the first adverse event (death or recurrence) or the latest follow up. OS and EFS were analyzed by Kaplan-Meier method. Ninety-five percent confidence intervals (CIs) were calculated for the survival estimation. This study was approved by the Ethics Committee of the Faculty of Pediatrics at Sheikh Khalifa Medical City (COA number Si.592/2013).

Results

A cohort of 14 children with hepatoblastoma managed in our institution between January 2009 and October 2019. There were 5 UAE National patients, and 9 Non-National ones. There were 6 male (42.9%) and 8 female (57.1%) children with a median age of 26.86 months at diagnosis in our institution between January 2009 and October 2019. Youngest patient diagnosed was 16 days old.

We reviewed the clinical presentation, serum α-fetoprotein level at diagnosis, histological subtype, treatment, and outcomes (Table-2). One patient had Edward syndrome and another patient had severe common immunodeficiency (SCID). 2 of our patients had history of transaminitis prior their diagnosis, and only one patient had significant family history of malignancy, remaining patients were previously healthy.

Of the 14 patients, 78.6% patients (11) were symptomatic at time of diagnosis, with abdominal mass being the most common presenting complains in 35% (Graph-1). The median AFP level at diagnosis was 10000 ng/mL. 57.1% patients (8) presented in stage 3 PRETEXT staging system. 2 were stage 4 with lung metastases. Right lobe of the liver was the commonest site in 8 patients and epithelial type, and epithelia mixed were the predominant histopathological subtypes in 10 patients 71.4%.

12 patients have received preoperative chemotherapy, followed by surgical resection; only one patient underwent upfront surgical resection followed by chemotherapy.

The one patient with an underlying diagnosis of Edwards syndrome was only for observation as tumor showed spontaneous regression. One patient underwent liver transplant. 12 patients underwent the recommended treatment protocol which utilizes 2-4 cycles of C5VD, followed by surgical resection. 3 of the patients who showed progression while on therapy in the form of distant metastases, or failure of primary tumor regression that is not amenable to surgical resection, underwent other modalities of therapies, including the use of the relapsed solid tumor regimen which consists of Gemcitabine 1000 mg/m2 IV, Bevacizumab (Avastin) 5-10 mg/kg IV on Day 1 of each cycle, and Oxlaliplatin 100 mg/m2 IV on Day 2. This was a 14-day cycle.

Liposomal Doxorubicin was not available in our institution, so Doxorubicin was tried on one patient, but had a reaction to it, so was discontinued.

Criteria of eligibility to start such therapy were Evidence of disease progression by both imaging studies and AFP level. Good performance scale using the Lansky or KARNOFSKY PERFORMANCE STATUS SCALE more than 70%. Hematological count recovery with absolute neutrophil count above

750 and Platelet count above 75,000, before each cycle. This was well tolerated with no major side effects from it. All patients received more than 6 months of this regimen, with acceptable performance.

2 out of the 3 patients did receive their planned chemotherapy on time, except one who had delayed count recovery, mainly thrombocytopenia.

All the 3 patients had shown stable disease while on this regimen. One patient went into apparent remission and travelled abroad where he received a live donor liver transplant. He was kept on Sorafenib post-transplant, but unfortunately, he relapsed after 3 months with disease progression and passed away.

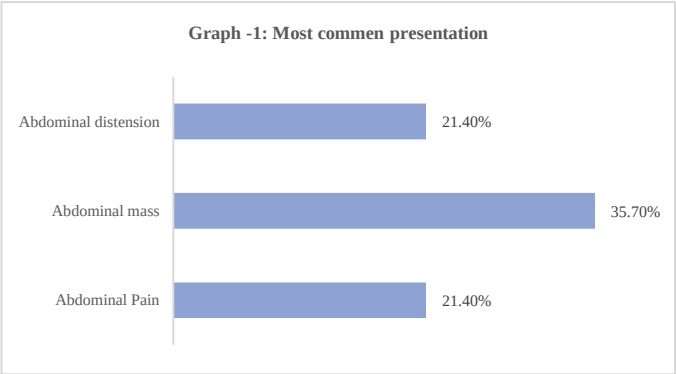
Other neoadjuvent experimental chemotherapy utilizing agents such as Pazopanib, Pembrolizumab and Sorafenib was used on one patient. She was stable for almost 6 months, before she progressed, and her condition deteriorated and passed away.

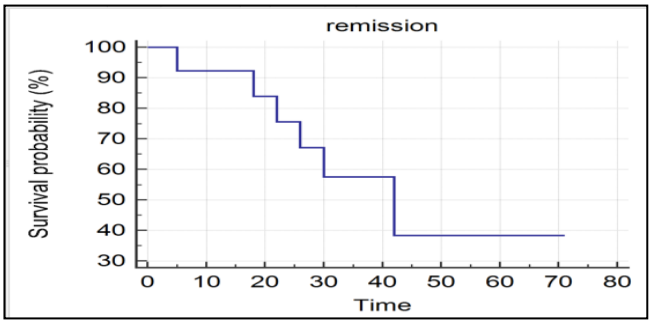
During follow-up, six patients died of progressive disease. Five of them had pulmonary metastases, and one had brain metastases. Only one patient underwent liver transplant, that was well tolerated, however he later on passed away due to tumor recurrence. The remaining patient are in remission until this day.

The median survival time was 42 months (95% confidence interval:18–42%). Five-year overall survival was 44.09% (95% confidence interval:18–42%), Graph-2.

Table -2. Demographic, clinical, radiological, and pathological characteristics of the study cohort

Median age at diagnosis in months, range	26 (0.52- 63)
Gender	
Male n (%)	6 (42.9)
Female n (%)	8 (57.1)
Median follow-up time in years, range	3.5 years (0.2-5.8)
AFP level (IU/ML)	
< 10,000	8 (57.1)
> 10,000	6 (42.9)
COG staging n (%)	
Stage I	1 (7.1)
Stage II	2 (14.3)
Stage III	8 (57.1)
Stage IV	3 (21.4)
Initial metastasis n (%)	
Lung	2 (14.3)
Bone	0
No metastasis	12 (85.7)
Pathological results n (%)	
Mixed epithelial and mesenchymal type	2 (14.3)
Pure fetal type	10 (71.4)
Embryonal type	2 (14.3)
Radiological findings of tumor location n (%)	
Right lobe	8 (57.1)
Left lobe	2 (14.3)
Unspecified	4 (28.6)





Graph -2. Kaplan-Meier survival analysis in months

Discussion

It is known that most hepatoblastoma can be diagnosed without a need for tumor biopsy, except for those who are younger than 6 months or older than 3 years, however in our center we opt to biopsy patients with high AFP levels, as previous studies have shown that elevated AFP could be linked to other diagnosis **[**5**]**.

The mainstay of treating hepatoblastoma varies widely between centers, neoadjuvant chemotherapy followed by resection has become the core in the treatment. With very effective preoperative chemotherapy for hepatoblastoma, many tumors can be shrunk to permit partial hepatectomy.

Total hepatectomy and liver transplantation has emerged as an effective treatment for the small proportion of children with unresectable hepatoblastoma that is limited to the liver **[**7**]**. A 5-year survival rate of 70% can be achieved in such cases.

However, for patients with unresectable hepatoblastoma, neoadjuvant chemotherapy is the only means to convert them into resectable tumors, through down-staging of the tumors **[**7,10**]**.

It is noteworthy that patients in our group had satisfactory results at early follow-up. Complete tumor resection is a prerequisite for cure, therefore, any strategy that leads to an increased resection rate will

result in improved survival. Surgical removal of hepatoblastoma is never easy, and resection-related deaths still occur even with experienced surgeons.

The introduction of chemotherapy to the neoadjuvant setting has helped to improve surgical resection rates. Our data also support an important role for preoperative neoadjuvant chemotherapy if the tumor is inoperable, or if the tumor is unlikely to undergo gross total resection at initial diagnosis **[**17**]**.

Data from our study showed that, in general, tumors of a lower stage had better 5-year EFS and OS rates than tumors of a higher stage; this was similar to the results of previous reports (Brown et al, 2000; Ortega et al, 2000; Fuchs et al, 2002; Perilongo et al, 2009; Zsiros et al,2010).

It is known that tumor metastasis, the outcomes of surgery, the initial AFP level and the pathological subtype are the important prognostic factors for hepatoblastoma (Haas et al,1989; von Schweinitz et al, 1995; van Tornout et al, 1997; Haas et al, 2001; Katzenstein et al,2002; Tomlinson and Finegold, 2006).

In our study, we also observed that patients who had complete tumor removal without microscopic residual disease had better survival, indicating the important role of radical surgery in treating hepatoblastoma.

Several reports have shown that a tumor with a pure fetal histology (PFH) had a better outcome, especially for those patients whose tumor could be completely resected (Haas et al,1989).

Ten patients (74.1%) in our study had a completely resected PFH subtype tumor. Despite having different treatment approaches or using different chemotherapy regimens, the patients in our study had 5-year EFS and OS rates comparable to those reported in studies from North America and Europe (Brown et al, 2000; Ortega et al, 2000; Fuchs et al, 2002; Perilongo et al, 2009; Zsiros et al, 2010).

Conclusion

Hepatoblastoma is the most common primary malignant liver neoplasm in children. Approximately 90% of the cases occur in patients under 5 years of age, and two thirds of the cases occur in the first 2 years of life.

Hepatoblastoma in adolescent and young adults is extremely rare nevertheless, the prognosis is much worse than in childhood, because these kinds of tumors are usually diagnosed late.

Some studies have shown a male to female ratio for hepatoblastoma patients of 3-2: 1. Hepatoblastoma's histopathology can be divided into two groups: epithelial type and mixed epithelial and mesenchymal type. The epithelial type consists of fetal and embryonic cells presenting alone or in combination; in the epithelio-mesenchymal mixed type, mesenchymal elements are present along with the epithelial component. Our patient's cohort followed the same distribution. The initial diagnosis of Hepatoblastoma (HB) is mainly based on imaging. Proper diagnosis, staging, and treatment of Hepatoblastoma require accurate imaging studies. Ultrasound (US) is a noninvasive modality that is particularly useful in the evaluation of infants. HB is seen as a hyperechoic, solid, intrahepatic mass on US. Other standard investigations include Computed tomography (CT), Magnetic Resonance imaging (MRI), and serum AFP. However, the final diagnosis relies on tumor biopsy. The complete surgical resection is the cornerstone of treatment for patients with HB and is the only chance of an optimal clinical result. Despite this, the improvements in survival that have occurred over the last three decades have been the function of standardized chemotherapy that reduces tumor size and enables complete tumor excision, even permitting cure in the presence of initially unresectable or metastatic disease**]**.

Chemotherapy has been proven effective in both an adjuvant and neoadjuvant treatment and can shrink tumors. It makes them less prone to bleed and delineates the tumor from the surrounding normal parenchyma and vascular structures to facilitate the resections. HB is sensitive to such chemotherapy drugs as Doxorubicin, Cisplatin, Vincristine, 5-FU.

In addition, in advanced stages, HB may show sensitivity to other forms of chemotherapy, like the regimen utilized on our patients who failed the conventional one. Targeted therapies also may have a role in prolongation life expectancy for those children with advanced disease while maintaining good quality of time for them and their families.

Further studies needed to be able to run on those new-targeted therapies to be able to validate the current data, in hope to integrate it in the future as part of standard therapies for advanced stages of hepatoblastoma.

References

1. Zhang Y, Zhang WL, Huang DS, Hong L, Wang YZ, Zhu X, et al. Clinical effectiveness of multimodality treatment on advanced pediatric hepatoblastoma. Eur Rev Med Pharmacol Sci. 2014;18((7)):1018–26.

2. Goodman ZD. Neoplasms of the liver. Mod Pathol 2007; 20 Suppl 1:S49.

3. Saxena R, Leake JL, Shafford EA et al. Chemotherapy effects on hepatoblastoma. A histological study. Am J Surg Pathol 1993;17:1266-1271.

4. Exelby PR, Filler RM, Grosfeld JL. Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey-1974. J Pediatr Surg 1975;10:329-337

5. Giardiello FM, Offerhaus GJ, Krush AJ et al. Risk of hepatoblastoma in familial adenomatous polyposis. J Pediatr 1991;119:766-768.

6. Haas JE, Muczynski KA, Krailo M et al. Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. Cancer 1989;64:1082-1095.

7. Perilongo G, Shafford E, Maibach R, et al: Risk-adapted treatment for childhood hepatoblastoma. final report of the second study of the International Society of Paediatric Oncology--SIOPEL 2. Eur J Cancer 40:411-21, 2004

8. Haas JE, Muczynski KA, Krailo M, et al: Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. Cancer 64:1082-95, 1989

9. Haas JE, Feusner JH, Finegold MJ: Small cell undifferentiated histology in hepatoblastoma may be unfavorable. Cancer 92:3130-4, 2001

10. Ortega JA, Krailo MD, Haas JE, et al: Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: a report from the Childrens Cancer Study Group. J Clin Oncol 9:2167-76, 1991

11. Brown J, Perilongo G, Shafford E, et al: Pretreatment prognostic factors for children with hepatoblastoma-- results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. Eur J Cancer 36:1418-25, 2000

12. Douglass EC, Green AA, Wrenn E, et al: Effective cisplatin (DDP) based chemotherapy in the treatment of hepatoblastoma. Med Pediatr Oncol 13:187-90, 1985

13. Black CT, Cangir A, Choroszy M, et al: Marked response to preoperative high-dose cis-platinum in children with unresectable hepatoblastoma. J Pediatr Surg 26:1070-3, 1991

14. Evans AE, Land VJ, Newton WA, et al: Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. Cancer 50:821-6, 1982

15. Van Tornout JM, Buckley JD, Quinn JJ, et al: Timing and magnitude of decline in alpha-fetoprotein levels in treated children with unresectable or metastatic hepatoblastoma are predictors of outcome: a report from the Children's Cancer Group. J Clin Oncol 15:1190-7, 1997

16. Vos A: Primary liver tumours in children. Eur J Surg Oncol 21:101-5, 1995

17. Tsay P, Lai J, Yang C, Hung I, Hsueh C, Tsai M et al. Treatment Outcomes for Hepatoblastoma: Experience of 35 Cases at a Single Institution. Journal of the Formosan Medical Association. 2011;110(5):322-325